

REMARKS

A. Status of the Claims

Claims 9-18 were pending at the time of the Action. Claim 9 has been amended to correct a typographical error. New claims 19-21 have been added. Thus, claims 9-21 are currently pending. Because the amendment to claim 9 merely corrected a typographical error recognized by the examiner (*see* Action, p. 4) and the new claims merely recite a narrower subset of the antioxidants A and antioxidants B recited in claim 9, any new grounds for rejection cannot be based on Applicant's amendment. Thus, it would be improper for a subsequent Office Action to be made final if it includes any new grounds for rejection. *See* MPEP § 706.07(a).

B. Oath/Declaration

The Action asserts that a new oath or declaration is required because the declaration as filed in the application is not in the English language. This assertion is incorrect. The present application is a U.S. nationalization of a PCT application under 35 U.S.C. § 371, and a declaration in accordance with PCT Rule 4.17(iv) was provided. 37 C.F.R. § 1.69(b) states that in a U.S. nationalization of a PCT application under 35 U.S.C. § 371, a translation is not required of a declaration provided in accordance with PCT Rule 4.17(iv).

C. The Claims Satisfy the Requirements of 35 U.S.C. § 112, ¶ 1 and 2

The Action rejects claims 9-18 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, and under 35 U.S.C. § 112, second paragraph, as being indefinite. The Action's asserted basis for both rejections is that the specification does not define the chemical names for the antioxidants represented by the abbreviations NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH. Applicant traverses these rejections.

A proper evaluation of claims 9-18 under the second paragraph of 35 U.S.C. § 112 requires that the claims be read in light of the specification as interpreted by one of ordinary skill

in the art. *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1579, 28 USPQ 2d 1333, 1339 (Fed. Cir. 1993). Whether a claim satisfies the written description requirement of the first paragraph of 35 U.S.C. § 112 is likewise determined from the perspective of a person of ordinary skill in the art. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). The current claims satisfy the requirements of 35 U.S.C. § 112, first and second paragraphs.

1. Well-Known Terms of Art Do Not Require Detailed Definitions

Use of well-known terms of art in the specification without detailed definitions does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58 (Fed. Cir. 1983). Claims may, therefore, make use of the language understood by those of skill in the art without additional, detailed definitions in the written description. *Id.* As described in more detail below, the terms NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH are well-known terms that are readily understood by those in the art. Thus, these terms do not require detailed definitions in the specification.

2. The Terms NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH Would Be Understood by Any Person Who Has Taken an Entry-Level Biochemistry Course

The Action clearly failed to examine the claims from the perspective of a person of ordinary skill in the art, as the terms NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH are well-known terms that are readily understood by those in the art. In fact, these terms would even be understood by those who have only taken an entry-level biochemistry course.

NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH are commonly used abbreviations for nicotinamide adenine dinucleotide, reduced form; nicotinamide adenine

dinucleotide phosphate, reduced form; flavin adenine dinucleotide, reduced form; flavin mononucleotide, reduced form; flavin adenine dinucleotide, radical form; and flavin mononucleotide, radical form; respectively. It is readily apparent from standard biochemistry text books that these abbreviations are commonly used and understood in the art. For example, attached as Exhibit B to the Declaration of Dr. Pfannhauser (“Pfannhauser Declaration”) (attached as Appendix A to this paper) is a table entitled “Some Common Biochemical Abbreviations” from Voet & Voet, BIOCHEMISTRY, 2d Ed., (John Wiley & Sons, Inc., 1995), which shows that NADH, NADPH, FADH₂, FADH, and FMN are well-known abbreviations in biochemistry. In fact, such abbreviations are used preferentially in Voet & Voet. If a person were to look up, for example, “nicotinamide adenine dinucleotide, reduced form” in the index of Voet & Voet that person would be directed to “see NADH.” The same is true of NADPH, FADH₂, FADH, and FMN. A highlighted copy of the relevant pages of the index is attached as Exhibit C to the Pfannhauser Declaration. Although the reduced and radical forms of FMN are not listed in the index, the terms FMNH₂ and FMNH are used in Voet & Voet at, for example, page 575 (Exhibit D to the Pfannhauser Declaration). Another undergraduate-level biochemistry text, Streyer, BIOCHEMISTRY, 3d Ed. (W.H. Freeman and Co., 1988) contains a table entitled “Common Abbreviations in Biochemistry,” which lists NADH, NADPH, FADH₂, FMNH₂, FAD, and FMN. A copy of this table is attached as Exhibit E to the Pfannhauser Declaration.

NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH are components of energy metabolism pathways (Pfannhauser Declaration, para. 5). NADH and FADH₂ are the major electron carriers in the oxidation of fuel molecules (Pfannhauser Declaration, para. 10). FAD may be fully reduced to FADH₂ or half-reduced to FADH (Pfannhauser Declaration, para. 10). NADPH is the major electron donor in reductive biosynthesis (Pfannhauser Declaration, para. 10). FMN is a component of Complex I of the mitochondrial electron transport chain

(Pfannhauser Declaration, para. 10). FMNH₂ is the reduced form of FMN and FMNH is the radical form of FMN (Pfannhauser Declaration, para. 10).

As stated in the Pfannhauser Declaration, energy metabolism pathways are learned by university students in their entry-level biochemistry courses (Pfannhauser Declaration, para. 5). Thus, even first-year university students who have taken an entry-level biochemistry course would readily understand the meaning of the terms NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH.

The Pfannhauser Declaration further notes that is clear from the present specification that NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH are described in the context of energy metabolism and electron transfer (Pfannhauser Declaration, para. 10). The Pfannhauser Declaration concludes that in view of the description of NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH in the present specification and the common use of these well-known terms in the biochemistry field, there is no question that scientists (and even students) in this field would readily understand the meaning of NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH as recited in the present claims and specification. (Pfannhauser Declaration, para. 11).

3. The Examiner Has Not Met His Burden

In rejecting a claim under the written description requirement, the Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined in the claims. *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976). Accordingly, the Examiner is required: (1) to set forth the claim limitation not described; and (2) to provide reasons why a person skilled in the art would not have recognized the description of the limitation in view of the disclosure of the application as filed. *Interim Guidelines for the Examination of Patent Applications Under 35*

U.S.C. 112, Paragraph 1. In making an indefiniteness rejection, the Examiner is required to provide an analysis as to why the claim is “vague and indefinite.” MPEP § 2173.02.

The only alleged reasoning provided to support the written description and definiteness rejections is that the abbreviations render the claims “totally unsearchable” because a person of ordinary skill in the art “would have no idea what one is searching and looking for.” (Action, p. 3; *see also* p. 4). It is unclear why the Examiner considers the terms NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH “totally unsearchable.” To demonstrate that these terms are in fact searchable, Applicant typed the search term “NADH” into the PubMed database on September 11, 2006. The search returned 39,521 articles. To obtain a more manageable number of results, the search was then limited to only those articles published in 2002 and in which “NADH” occurred in the title. With these limitations the search returned 124 articles. A copy of the search results is attached as Appendix B. Numerous results were also obtained when Applicant searched the PubMed database for any of the terms NADPH, FADH₂, FMNH₂, FADH, or FMNH. The Action’s unsupported assertion that the claims are “totally unsearchable” is clearly inaccurate. Thus, the Action did not meet its burden of establishing that the claims do not satisfy the definiteness and written description requirements.

4. Conclusion

For the reasons set forth above, the present claims are definite and supported by adequate written description. Applicant, therefore, requests the withdrawal of these rejections.

D. Claim Objections

Claim 10 is objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant traverses this objection.

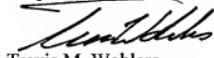
An antioxidant is a compound that inhibits oxidation by binding free oxygen radicals. As recited in claim 9, antioxidant A is NADH, NADPH, FADH₂, FMNH₂, FADH, or FMNH; and antioxidant B is chlorophyll and/or a reduced ferredoxin. An “oxygen-sequestering substance” is a substance, such as an oil, that reduces, or largely prevents, any contact between antioxidant A and oxygen (Specification, p. 6, ln. 1-22). As described in the specification, an “oxygen-sequestering substance” protects antioxidant A by preventing the *contact* of antioxidant A with oxygen, whereas another antioxidant (i.e., antioxidant C) protects antioxidant A by *reducing oxygen* before the oxygen can react with antioxidant A (p. 6, ln. 23-32). Thus, claim 10 is a proper dependent claim because it references claim 9 and specifies a further limitation, namely that the composition of claim 9 further comprise an oxygen-sequestering substance, which is not the same substance as antioxidant A or antioxidant B as defined in current claim 9.

E. Conclusion

Applicant believes this to be a complete reply to the Office Action dated June 21, 2006, and respectfully requests favorable consideration of the claims in view of the amendments and statements contained herein.

The Examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Date: September 15, 2006

APPENDIX A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Behzad SADEGHI *et al.*

Serial No.: 10/535,330

Filed: May 18, 2005

For: NADH/NADPH-CONTAINING COMPOUND

Group Art Unit: 1714

Examiner: Anthony, Joseph David

Atty. Dkt. No.: SONN:073US

DECLARATION OF WERNER PFANNHAUSER, Ph.D.

I, Werner Pfannhauser, hereby declare as follows:

1. I am an Austrian citizen residing at Kreuzgasse 79, A - 1180 Vienna, Austria.
2. I am currently the head of the Institute of Food Chemistry and Technology at the Technical University of Graz in Graz, Austria. I have extensive experience in the fields of chemistry and biochemistry. A copy of my *Curriculum Vitae* is attached as Exhibit A.
3. I have reviewed the specification of the above-referenced application, the currently pending claims, the amended set of claims, and the Office Action dated June 21, 2006.
4. I understand that the Examiner rejected claims 9-18 as being indefinite and lacking adequate written description. I understand that the Examiner asserts that because the specification does not define the chemical names for the abbreviations NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH, a person of ordinary skill in the art would not understand the meaning of these terms. I do not find this to be the case.

5. The terms NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH are well-known in the field of biochemistry as they are components of energy metabolism pathways. In my experience, both as a student and as a professor, energy metabolism pathways (e.g., glycolysis, citric acid cycle, and oxidative phosphorylation) are taught to university students in their entry-level biochemistry courses. As evidence of this, I have attached as Exhibits B-G pages from two general biochemistry text books: Voet & Voet, BIOCHEMISTRY, 2d Ed., (John Wiley & Sons, Inc., 1995) and Streyer, BIOCHEMISTRY, 3d Ed. (W.H. Freeman and Co., 1988).

6. Exhibit B is a table entitled "Some Common Biochemical Abbreviations" from Voet & Voet, which shows that NADH, NADPH, FADH₂, FADH, and FMN are well-known abbreviations in biochemistry. Exhibit C contains pages from the index of Voet and Voet listing NADH, NADPH, FADH₂, FADH, and FMN. Although the reduced and radical forms of FMN are not listed in the index, FMNH₂ and FMNH are described in Voet & Voet at, for example, page 575 (Exhibit D). Exhibit E is a table from the Streyer text book entitled "Common Abbreviations in Biochemistry," which lists NADH, NADPH, FADH₂, FMNH₂, FAD, and FMN.

7. Exhibit F contains pages 785 to 788 from Voet & Voet and provides a summary of the major energy metabolism pathways. NADH, NADPH, and FADH₂ are specifically mentioned on these pages. I also note that they are referred to as "NADH," "NADPH," and "FADH₂" and not as "nicotinamide adenine dinucleotide, reduced form," "nicotinamide adenine dinucleotide phosphate, reduced form," and "flavin adenine dinucleotide, reduced form." FADH is described on pages 400-401 of Voet & Voet (Exhibit G). FMNH₂ and FMNH are described on page 575 of Voet & Voet (Exhibit D).

8. Accordingly, anyone who has taken an entry-level biochemistry course would readily understand the meaning of the terms NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH. Of course, scientists who conduct research in this field would also readily understand the meaning of these terms.

9. Although the compounds NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH may also be referred to as nicotinamide adenine dinucleotide, reduced form; nicotinamide adenine dinucleotide phosphate, reduced form; flavin adenine dinucleotide, reduced form; flavin mononucleotide, reduced form; flavin adenine dinucleotide, radical form; and flavin mononucleotide, radical form, respectively; it is has been my experience from the scientific literature and from communications with my colleagues and students that NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH are the more commonly used terms. The preferred use of the terms NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH is evident in Voet & Voet. For example, if a person looks up "nicotinamide adenine dinucleotide, reduced form" in the index of Voet & Voet (attached as Exhibit D) that person would be directed to "see NADH." The same is true of NADPH, FADH₂, FADH, and FMN.

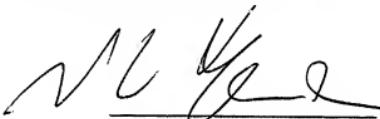
10. From my review of the present specification, it is clear that NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH are described in the context of energy metabolism and electron transfer. As explained in the preceding paragraphs, it is well-known that NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH are components of energy metabolism pathways (*see also* Exhibits B-G). In particular, it is well-known that NADH and FADH₂ are the major electron carriers in the oxidation of fuel molecules, and that FAD may be fully reduced to FADH₂ or half-reduced to FADH. NADPH is the major electron donor in reductive biosynthesis. FMN is a

component of Complex I of the mitochondrial electron transport chain and FMNH₂ is the reduced form of FMN and FMNH is the radical form of FMN.

11. In view of the description of NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH in the present specification and the common use of these well-known terms in the biochemistry field, there is no question that scientists (and even students) in this field would readily understand the meaning of NADH, NADPH, FADH₂, FMNH₂, FADH, and FMNH as recited in the present claims and specification.

12. I declare that all statements made of my knowledge are true and all statements made on the information are believed to be true; and, further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereupon.

Date: 13.9.2006



Werner Flannhauser, Ph.D.

EXHIBIT A

O.Univ.Prof. Dr. Werner Pfannhauser
Institute of Food Chemistry and -technology, University of Technology Graz
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A - 1180 Wien, Kreuzgasse 79

C U R R I C U L U M

7.6.1940	born in Vienna / Austria
2.6.1959	Matura BG XVIII Vienna
1.9.1963 - 31.8.1965	Employee (research contract) at Wienerberger Ziegeleifabriks- und Baugesellschaft, Vienna, working at TGM (Higher technical School)
1.9.1963 - 31.8.1969	Assistsant at TGM (Higher Technical School), Department of Silica Techniques
1969	Grant for gifted students
1969 - 1971	Thesis at Institute of Analytical Chemistry (Univ.Prof. F. Hecht) University of Vienna
8.7.1971	Promotion
24.1.1971	Titel Engeneer (Ing)
16.8.1971 -	Chemist, Senior Scientist (1974) and Vizedirektor (1981) of
31.8.1993	Forschungsinstitut der Ernährungswirtschaft (Research Institute of the Food Industry), Vienna
1978	Research Grant of the City of Vienna
1979 - 1996	Secretary of the Federation of European Chemical Societies (FECS) Working Party of Food Chemistry (WPFC), now renamed Division of Food Chemistry
since 1994	Austrian Delegate in FECS / FCD
since 1984	Board Member of the Austrian Society of Analytical Chemistry (ASAC),
since 1991	Vice President of ASAC
7.12.1988	Habilitation for Analytical Chemistry ar Technical University of Vienna
since 1992	Chairman of the Working Party of Food Chemistry of the Austrian Chemical Society (GÖCh)
1.10.1993	Appointed as a Full Professor of Food Chemistry at the Technical University of Graz, Institute of Bio- and Food Chemistry
1995 - 1998	Scientific director of Lebensmittelversuchsanstalt and Forschungsinstitut der Ernährungswirtschaft, Vienna
September 1996	Editor of Ernährung / nutrition
1996 -2000	President of the Austrian Society of Nutrition (ÖGE)
11/2000	Head of the newly founded Institute of Food Chemistry and - technology

Private:

married with Dkfm. Gertraud Pfannhauser, born Gruber, 5 sons;
Owner of a private consulting agency in Vienna

Distinctions:

1988 : Gold Medal of the Italian Society of Flavour Research (Societa Scienze Aromatizzanti SSA)

1994 : Silver Medal of Merit of The City of Vienna

P U B L I K A T I O N S L I S T E

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1991

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EXHIBIT B

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BIOCHEMISTRY

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Cover Art: Two paintings of horse heart cytochrome c by Irving Geis in which the protein is illuminated by its single iron atom. On the front cover the hydrophilic side chains are drawn in green, and on the back cover the hydrophobic side chains are drawn in orange. The paintings are based on an X-ray structure by Richard Dickerson.

SOME COMMON BIOCHEMICAL ABBREVIATIONS^a

A	adenine	ER	endoplasmic reticulum
aa	amino acid	FAD	flavin adenine dinucleotide, oxidized form
aaRS	amino-acyl tRNA synthetase	FADH _·	flavin adenine dinucleotide, radical form [†]
ACAT	acyl-CoA:cholesterol acyl transferase	FADH ₂	flavin adenine dinucleotide, reduced form
ACh	acetylcholine	FBP	fructose-1,6-bisphosphate
ACP	acyl carrier protein	FBPase	fructose-1,6-biphosphatase
ADA	adenosine deaminase	Fd	ferredoxin
ADH	alcohol dehydrogenase	FH	familial hypercholesterolemia
ADP	adenosine diphosphate	fMet	<i>N</i> -formylmethionine
AIDS	acquired immunodeficiency syndrome	FMN	flavin mononucleotide [‡]
AMP	adenosine monophosphate	F1P	fructose-1-phosphate
AMPK	AMP-dependent protein kinase	F6P	fructose-6-phosphate
ALA	δ -aminolevulinic acid	G	guanine
ATCase	aspartate transcarbamoylase	GABA	γ -aminobutyric acid
ATP	adenosine triphosphate	Gal	galactose
BChl	bacteriochlorophyll	GalNAc	<i>N</i> -acetylgalactosamine
bp	base pair	GAP	glyceraldehyde-3-phosphate
BPG	d-2,3-bisphosphoglycerate	GAPDH	glyceraldehyde-3-phosphate dehydrogenase
BPho	bacteriopheophytin	GC	gas chromatography
BPTI	bovine pancreatic trypsin inhibitor	GDP	guanosine diphosphate
C	cytosine	Glc	glucose
CaM	calmodulin	GMP	guanosine monophosphate
cAMP	cyclic AMP	G1P	glucose-1-phosphate
CAP	catabolite gene activating protein	G6P	glucose-6-phosphate
cAPK	cAMP-dependent protein kinase	GPI	glycosylphosphatidyl inositol
cDNA	complimentary DNA	GSH	glutathione
CDP	cytidine diphosphate	GSSG	glutathione disulfide
CDR	complimentary determining region	GTP	guanosine triphosphate
CE	capillary electrophoresis	HA	hemagglutinin
Chl	chlorophyll	Hb	hemoglobin
CM	carboxymethyl	HDL	high density lipoprotein
CMP	cytidine monophosphate	HPRT	hypoxanthine-guanine phosphoribosyl transferase
CoA or CoASH	coenzyme A	HIV	human immunodeficiency virus
CoQ	coenzyme Q (ubiquinone)	HMG-CoA	β -hydroxy- β -methylglutaryl-CoA
CTP	cytidine triphosphate	hnRNA	heterogeneous nuclear RNA
D	dalton	HPLC	high-performance liquid chromatography
d	deoxy	hsp	heat shock protein
dd	dideoxy	Hyl	5-hydroxylysine
DEAE	diethylaminoethyl	Hyp	4-hydroxyproline
DG	<i>sn</i> -1,2-diacylglycerol	IDL	intermediate density lipoprotein
DHAP	dihydroxyacetone phosphate	IF	initiation factor
DHF	dihydrofolate	IgG	immunoglobulin G
DHFR	dihydrofolate reductase	IHP	inositol hexaphosphate
DMF	<i>N,N</i> -dimethylformamide	IMP	inosine monophosphate
DMS	dimethyl sulfate	IP ₁	inositol-1-phosphate
DNP	2,4-dinitrophenol	IP ₃	inositol 1, 4, 5-triphosphate
DNA	deoxyribonucleic acid	IFTG	isopropylthiogalactoside
Dol	dolichol	IR	infrared
L-DOPA	L-3,4-dihydroxyphenylalanine	IS	insertion sequence
EF	elongation factor	ITP	inosine triphosphate
EGF	epidermal growth factor	K _M	Michaelis constant
EPR	electron paramagnetic resonance	kb	kilo base pair

^a The three-letter and one-letter abbreviations for the "standard" amino acid residues are given in Table 4-1.

kD	kilodaltons	PRPP	5-phosphoribosyl- α -pyrophosphate
KF	Klenow fragment	PS	photosystem
LCAT	lecithin:cholesterol acyl transferase	PSTV	potato spindle tuber virus
LDH	lactate dehydrogenase	Q	ubiquinone (CoQ)
LDL	low density lipoprotein	QH ₂	ubiquinol
Man	mannose	r	ribo
Mb	myoglobin	RER	rough endoplasmic reticulum
MHC	major histocompatibility complex	RF	release factor or replicative form
mRNA	messenger RNA	RFLP	restriction-fragment length polymorphism
MS	mass spectrometry	RK	HMG-CoA reductase kinase
NA	neuraminidase	RNA	ribonucleic acid
NAD^+	nicotinamide adenine dinucleotide, oxidized form ^a	RNAP	RNA polymerase
NADH	nicotinamide adenine dinucleotide, reduced form ^a	RSP	ribose-5-phosphate
NADP^+	nicotinamide adenine dinucleotide, phosphate, oxidized form ^a	RPC	reverse phase chromatography
NADPH	nicotinamide adenine dinucleotide phosphate, reduced form ^a	rRNA	ribosomal RNA
NAG	N-acetylglucosamine	RSV	Rous sarcoma virus
NAM	N-acetylmuramic acid	RT	reverse transcriptase
NANA	N-acetylneurameric (sialic) acid	RTK	receptor tyrosine kinase
NER	nucleotide excision repair	Ru1,5P	ribulose-1,5-bisphosphate
NMN	nicotinamide mononucleotide	Ru5P	ribulose-5-phosphate
NMR	nuclear magnetic resonance	S	Svedberg unit
NOESY	nuclear Overhauser effect spectroscopy	SAM	S-adenosylmethionine
P or p	phosphate	SCID	severe combined immunodeficiency disease
P _i	orthophosphate ion	SDS	sodium dodecyl sulfate
PAGE	polyacrylamide gel electrophoresis	snRNA	small nuclear RNA
PBG	porphobilinogen	snRNP	small ribonuclear protein
PC	plastocyanin	S7P	sedoheptulose-7-phosphate
PCR	polymerase chain reaction	SRP	signal recognition particle
PE	phosphatidylethanolamine	T	thymine
PEP	phosphoenolpyruvate	TBP	TATA box-binding protein
PEPCK	PEP carboxykinase	TBSV	tomato bushy stunt virus
PFG	pulsed-field gel electrophoresis	TCA	tricarboxylic acid
PFK	phosphofructokinase	THF	tetrahydrofolate
PG	prostaglandin	TIM	triose phosphate isomerase
2PG	2-phosphoglycerate	TLC	thin layer chromatography
3PG	3-phosphoglycerate	TMV	tobacco mosaic virus
PDGF	platelet-derived growth factor	TPP	thiamine pyrophosphate
PGI	phosphogluco isomerase	tRNA	transfer RNA
PGK	phosphoglycerate kinase	TS	thymidylate synthase
PGM	phosphoglycerate mutase	TTP	thymidine triphosphate
Pheo	pheophytin	U	uracil
PIP ₂	phosphatidylinositol-4,5-bisphosphate	UDP	uridine diphosphate
PK	pyruvate kinase	UDPG	UDP-glucose
PKU	phenylketonuria	UMP	uridine monophosphate
PLP	pyridoxal-5-phosphate	UTP	uridine triphosphate
PNP	purine nucleotide phosphorylase	UV	ultraviolet
Pol	DNA polymerase	V_{\max}	maximal velocity
PP _i	pyrophosphate ion	VLDL	very low density lipoprotein
PrP	prion protein	XMP	xanthosine monophosphate
		XP	xeroderma pigmentosum
		Xu5P	xylulose-t-phosphate
		YAC	yeast artificial chromosome
		YADH	yeast alcohol dehydrogenase

EXHIBIT C

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BIOCHEMISTRY

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Cover Art: Two paintings of horse heart cytochrome c by Irving Geis in which the protein is illuminated by its single iron atom. On the front cover the hydrophilic side chains are drawn in green, and on the back cover the hydrophobic side chains are drawn in orange. The paintings are based on an X-ray structure by Richard Dickerson.

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EXHIBIT D

DONALD VOET

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Cover Art: Two paintings of horse heart cytochrome c by Irving Geis in which the protein is illuminated by its single iron atom. On the front cover the hydrophilic side chains are drawn in green, and on the back cover the hydrophobic side chains are drawn in orange. The paintings are based on an X-ray structure by Richard Dickerson.

O_2 consumes twice as many moles of NADH as of O_2 , the P/O ratio for NADH reoxidation at Region 2 is 90 $\mu\text{mol of ADP}/(2 \times 15 \mu\text{mol of } O_2) = 3$; that is, 3 mol of *ADP are phosphorylated per mole of NADH oxidized*.

(b) The experiment is continued by inhibiting electron transfer from NADH by rotenone and adding an additional 90 $\mu\text{mol of ADP}$ (Fig. 20-12; Region 4), this time together with an excess of the FAD-linked substrate succinate. Oxygen consumption again continues until all the ADP is phosphorylated, and the system again returns to the resting state (Fig. 20-12; Region 5). Calculation of the P/O ratio for FADH_2 oxidation yields the value 2; that is, 2 mol of *ADP are phosphorylated per mole of FADH_2 oxidized*.

(c) In the same manner, the oxidation of ascorbate/TMPD yields a P/O ratio of 1 (Fig. 20-12; Regions 6 and 7).

These conclusions agree with the inhibitor studies indicating that there are three entry points for electrons into the electron-transport chain and with the standard reduction potential measurements exhibiting three potential jumps, each sufficient to provide the free energy for ATP synthesis (Fig. 20-8).

The P/O Ratios May Be Subject to Revision

Measurements of P/O ratios are subject to systematic experimental errors for which it is difficult to correct, such as inaccuracies in the measurement of the oxygen concentration, the presence of AMP, and proton leakage from mitochondria. Thus, the widely accepted P/O values of 3, 2, and 1 associated with NADH-, FADH_2 -, and ascorbate/TMPD-linked oxidation may well be in error. Indeed, measurements by Peter Hinkle have yielded values close to 2.5, 1.5, and 1 for these quantities (we shall see in Section 20-3 that P/O ratios need not have integer values because the number of protons pumped out of the mitochondrion by any component of the electron transport chain may not be an integer multiple of the number of protons required to

synthesize ATP from $\text{ADP} + \text{P}_i$). If these values are correct, then the number of ATPs that are synthesized per molecule of glucose oxidized is $2.5 \text{ ATP}/\text{NADH} \times 10 \text{ NADH}/\text{glucose} + 1.5 \text{ ATP}/\text{FADH}_2 \times 2 \text{ FADH}_2/\text{glucose} + 2 \text{ ATP}/\text{glucose}$ from the citric acid cycle + 2 ATP/glucose from glycolysis = 32 ATP/glucose rather than the conventional value of 38 ATP/glucose implied by P/O ratios of 3, 2, and 1. However, since there is significant disagreement as to the validity of the revised P/O ratios, we shall, for the sake of consistency, use the more established values of 3, 2, and 1 throughout this textbook. You should nevertheless keep in mind that these values are disputed.

How the free energy of electron transport is actually coupled to ATP synthesis, a subject of active research, is discussed in Section 20-3. We first examine the structures of the four respiratory complexes in order to understand how they are related to the function of the electron-transport chain. Keep in mind, however, that as in most areas of biochemistry, this field is under intense investigation and much of the information we need for a complete understanding of these relationships has yet to be uncovered.

C. Components of the Electron-Transport Chain

Many of the proteins embedded in the inner mitochondrial membrane are organized into the four respiratory complexes of the electron-transport chain. Each complex consists of several protein components that are associated with a variety of redox-active prosthetic groups with successively increasing reduction potentials (Table 20-1). The complexes are all laterally mobile within the inner mitochondrial membrane; they do not appear to form any stable higher structures. Indeed, they are not present in equimolar ratios. In the following paragraphs, we examine their structures and the agents that transfer electrons between them. Their relationships are summarized in Fig. 20-13.

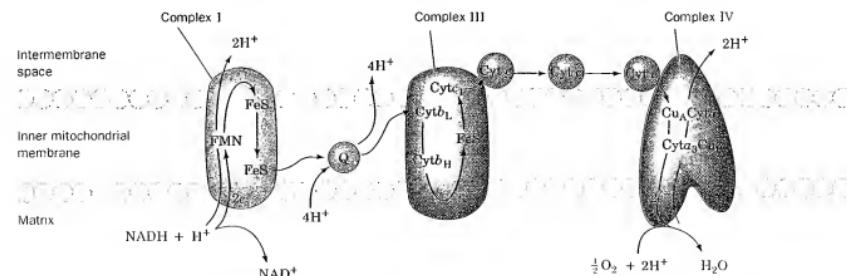


FIGURE 20-13. A diagram of the mitochondrial electron-transport chain indicating the pathway of electron transfer (black) and proton pumping (red). Electrons are transferred between Complexes I and III by the membrane-soluble CoQ

and between Complexes III and IV by the peripheral membrane protein cytochrome *c*. Complex II (not shown) transfers electrons from succinate to CoQ .

1. Complex I (NADH–Coenzyme Q Reductase)

Complex I passes electrons from NADH to CoQ. This probably largest protein component of the inner mitochondrial membrane (850 kD) contains one molecule of flavin mononucleotide (FMN; redox-active prosthetic group that differs from FAD only by the absence of the AMP group) and six to seven iron–sulfur clusters that participate in the electron-transport process (Table 20-1).

Iron–Sulfur Clusters Are Redox Active

Three types of iron–sulfur clusters are known to occur as prosthetic groups of iron–sulfur proteins (nonheme iron proteins):

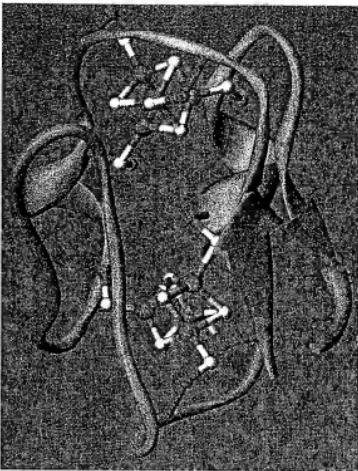
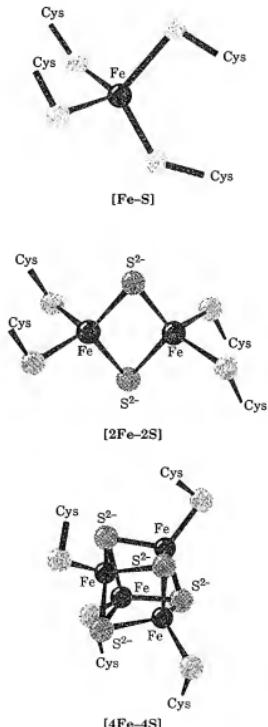


FIGURE 20-14. The X-ray structure of ferredoxin from *Peptococcus aerogenes*, a monomeric 54-residue protein that contains two [4Fe–4S] clusters. The C_β atoms of the four Cys residues liganding each [4Fe–4S] cluster are green, the Fe atoms are brown, and the S atoms are yellow. [Based on an X-ray structure by Elinor Adman, Larry Sieker, and Lyle Jensen, University of Washington.]

utilizes the fact that their sulfide ions are acid labile: They are released as H₂S near pH 1. The [Fe–S] cluster, which has been found only in bacteria, consists of a single Fe atom liganded to four Cys residues. Note that the Fe atoms in all three types of clusters are each coordinated by four S atoms, which are more or less tetrahedrally disposed around the Fe. (A [3Fe–4S] cluster, which has been found in only one bacterial species, resembles a [4Fe–4S] cluster that lacks an Fe atom.) The oxidized and reduced states of all iron–sulfur clusters differ by one formal charge regardless of their number of Fe atoms. This is because the Fe atoms in each cluster form a conjugated system and thus can have oxidation states between the +2 and +3 values possible for individual Fe atoms. For example, each of the two [4Fe–4S] clusters in the protein ferredoxin (Fig. 20-14) contains one Fe(II) and three Fe(III)'s in its oxidized form and two Fe(II)'s and two Fe(III)'s in its reduced form. Iron–sulfur proteins also occur in the photosynthetic electron-transport chains of plants and bacteria (Section 22-2); indeed, photosynthetic electron-transport chains are thought to be the evolutionary precursors of oxidative electron-transport chains (Section 1-4C).

The two most common types, designated [2Fe–2S] and [4Fe–4S] clusters, consist of equal numbers of iron and sulfide ions and are both coordinated to four protein Cys sulfhydryl groups. One means of identifying these clusters

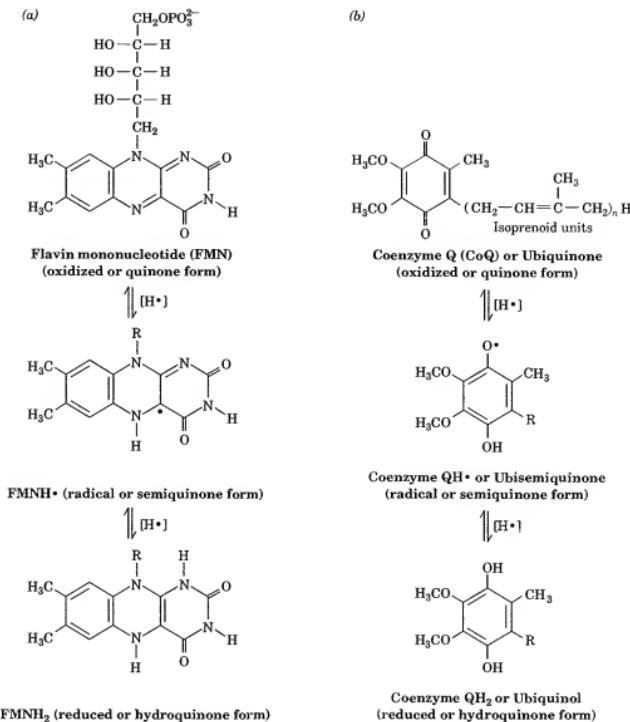


FIGURE 20-15. The oxidation states of (a) FMN and (b) CoQ. Both coenzymes form stable semiquinone free radical states.

The Coenzymes of Complex I

FMN and CoQ, the coenzymes of Complex I, can each adopt three oxidation states (Fig. 20-15). Although NADH can only participate in a two-electron transfer, both FMN and CoQ are capable of accepting and donating either one or two electrons because their semiquinone forms are stable. In contrast, the cytochromes of Complex III (see below), to which reduced CoQ passes its electrons, are only capable of one-electron reductions. *FMN and CoQ therefore provide an electron conduit between the two-electron donor NADH and the one-electron acceptors, the cytochromes.*

CoQ's hydrophobic tail makes it soluble in the inner mitochondrial membrane's lipid bilayer. In mammals, this tail consists of 10 C₅ isoprenoid units and hence the coen-

zyme is designated Q₁₀. In other organisms, CoQ may have only 6 (Q₆) or 8 (Q₈) isoprenoid units.

2. Complex II (Succinate–Coenzyme Q Reductase)

Complex II, which contains the dimeric citric acid cycle enzyme succinate dehydrogenase (Section 19-3F) and three other small hydrophobic subunits, passes electrons from succinate to CoQ. It does so with the participation of a covalently bound FAD, one [4Fe–4S] cluster, two [2Fe–2S] clusters, and one cytochrome b₅₆₀ (Table 20-1). We discuss the structures of the cytochromes in connection with that of Complex III below. [One of Complex II's iron–sulfur clusters has a standard reduction potential that is too negative (−0.245 V) to accept electrons from succinate; its function is unknown.]

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COMMON ABBREVIATIONS IN BIOCHEMISTRY

A	adenine	Hyp	hydroxyproline
ACP	acyl carrier protein	IgG	immunoglobulin G
ADP	adenosine diphosphate	Ile	isoleucine
Ala	alanine	IP ₃	inositol trisphosphate
AMP	adenosine monophosphate	ITP	inosine triphosphate
cAMP	cyclic AMP	LDL	low-density lipoprotein
cGMP	cyclic GMP	Leu	leucine
Arg	arginine	Lys	lysine
Asn	asparagine	Met	methionine
Asp	aspartate	NAD ⁺	nicotinamide adenine dinucleotide [§] (oxidized form) [§]
ATP	adenosine triphosphate	NADH	nicotinamide adenine dinucleotide [§] (reduced form) [§]
ATPase	adenosine triphosphatase	NADP ⁺	nicotinamide adenine dinucleotide [§] phosphate (oxidized form) [§]
C	cytosine	NADPH	nicotinamide adenine dinucleotide [§] phosphate (reduced form) [§]
CDP	cytidine diphosphate	PFK	phosphofructokinase
CMP	cytidine monophosphate	Phe	phenylalanine
CTP	cytidine triphosphate	P _i	inorganic orthophosphate
CoA	coenzyme A	PLP	pyridoxal phosphate
CoQ	coenzyme Q (ubiquinone)	PP _i	inorganic pyrophosphate
cyclic AMP	adenosine 3',5'-cyclic monophosphate	Pro	proline
cyclic GMP	guanosine 3',5'-cyclic monophosphate	PRPP	phosphoribosylpyrophosphate
Cys	cysteine	Q	ubiquinone (or plastoquinone)
cyt	cytochrome	OH ₂	ubiquinol (or plastoquinol)
d	2'-deoxyribo	RNA	ribonucleic acid
DNA	deoxyribonucleic acid	mrRNA	messenger RNA
cDNA	complementary DNA	rRNA	ribosomal RNA
Dnase	deoxyribonuclease	scRNA	small cytoplasmic RNA
EcoRI	EcoRI restriction endonuclease	snRNA	small nuclear RNA
FAD	flavin adenine dinucleotide (oxidized form)	tRNA	transfer RNA
FADH ₂	flavin adenine dinucleotide [§] (reduced form) [§]	RNase	ribonuclease
fMET	formylmethionine	Rubisco	ribulose 1,5-bisphosphate carboxylase
FMN	flavin mononucleotide (oxidized form) [§]	Ser	serine
FMNH ₂	flavin mononucleotide (reduced form) [§]	T	thymine
G	guanine	Thr	threonine
Gln	glutamine	TPP	thiamine pyrophosphate
Glu	glutamate	Trp	tryptophan
Gly	glycine	TTT	thymidine triphosphate
GDP	guanosine diphosphate	Tyr	tyrosine
GMP	guanosine monophosphate	U	uracil
GSH	reduced glutathione	UDP	uridine diphosphate
GSSG	oxidized glutathione	UDP-galactose	uridine diphosphate galactose
GTP	guanosine triphosphate	UDP-glucose	uridine diphosphate glucose
GTPase	guanosine triphosphatase	UMP	uridine monophosphate
Hb	hemoglobin	UTP	uridine triphosphate
HDL	high-density lipoprotein	Val	valine
HPRT	hypoxanthine-guanine phosphoribosyl transferase	VLDL	very low-density lipoprotein
His	histidine		

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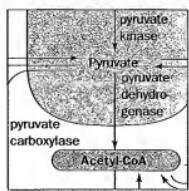
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25

Energy Metabolism: Integration and Organ Specialization

1. Major Pathways and Strategies of Energy Metabolism: A Summary
2. Organ Specialization
 - A. Brain
 - B. Muscle
 - C. Adipose Tissue
 - D. Liver
3. Metabolic Adaptation
 - A. Starvation
 - B. Diabetes Mellitus

At this point in our narrative we have studied all of the major pathways of energy metabolism. Consequently, we are now in a position to consider how organisms, mammals in particular, orchestrate the metabolic symphony to meet their energy needs. This chapter therefore begins with a recapitulation of the major metabolic pathways and their control systems, then considers how these processes are apportioned among the various organs of the body, and ends with a discussion of how the body deals with the metabolic challenge of starvation and how it responds to the loss of control resulting from diabetes mellitus.

1. MAJOR PATHWAYS AND STRATEGIES OF ENERGY METABOLISM: A SUMMARY

Figure 25-1 indicates the interrelationships among the major pathways involved in energy metabolism. Let us review these pathways and their control mechanisms.

1. Glycolysis (Chapter 16)

The metabolic degradation of glucose begins with its conversion to two molecules of pyruvate with the net generation of two molecules each of ATP and NADH. Under anaerobic conditions, pyruvate is converted to lactate (or, in yeast, to ethanol) so as to recycle the NADH. Under aerobic conditions, however, when glycolysis serves to prepare glucose for further oxidation, the NAD⁺ is regenerated through oxidative phosphorylation (see below). The flow of metabolites through the glycolytic pathway is largely controlled by the activity of phosphofructokinase (PFK). This enzyme is activated by AMP and ADP, whose concentrations rise as the need for energy metabolism increases, and is inhibited by ATP and citrate, whose concentrations increase when the demand for energy metabolism has slackened. PFK is also activated by fructose-2,6-bisphosphate, whose concentration is regulated by the levels of glucagon, epinephrine, and norepinephrine through the intermediacy

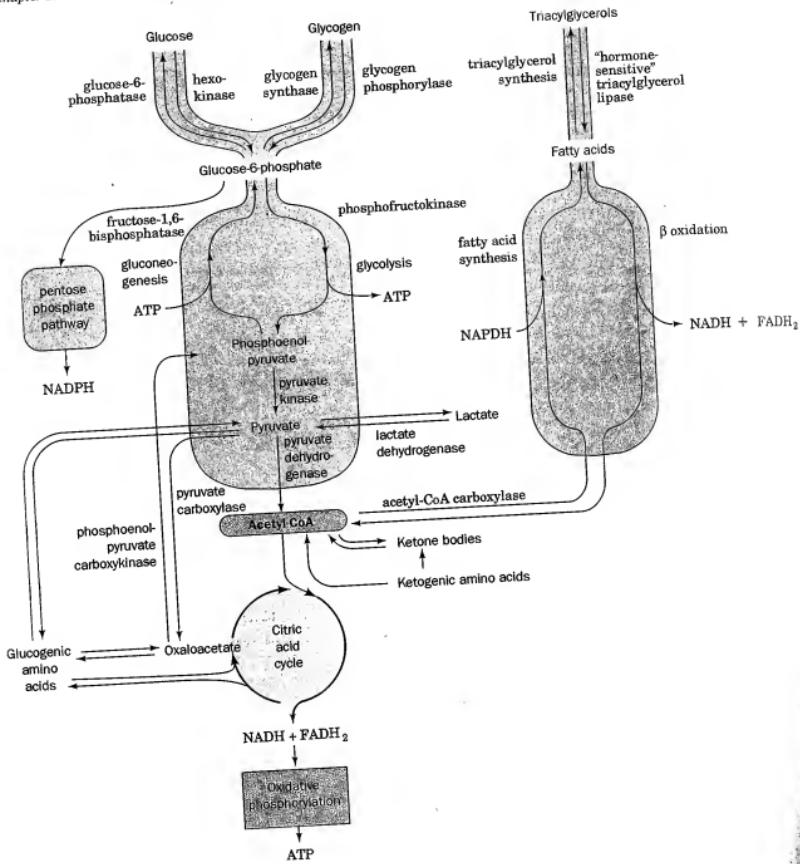


FIGURE 25-1. The major energy metabolism pathways.

of cAMP (Section 17-3F). Liver and heart muscle F2,6P levels are regulated oppositely: A [cAMP] increase causes an [F2,6P] decrease in liver and an [F2,6P] increase in heart muscle.

2. Gluconeogenesis (Section 21-1)

Mammals can synthesize glucose from a variety of precursors, including pyruvate, lactate, glycerol, and glucogenic amino acids, through pathways that occur mainly in liver and kidney. Many of these precursors are converted to oxaloacetate which, in turn, is converted to

phosphoenolpyruvate and then, through a series of reactions that largely reverse the path of glycolysis, to glucose. The irreversible steps of glycolysis, those catalyzed by PFK and hexokinase, are bypassed in gluconeogenesis by hydrolytic reactions catalyzed, respectively, by fructose-1,6-bisphosphatase (FBPase) and glucose-6-phosphatase. FBPase and PFK may both be at least partially active simultaneously, creating a substrate. This cycle, and the reciprocal regulation of PFK and FBPase, are important in regulating both the

direction of flux through glycolysis and gluconeogenesis (Sections 16-3 and 21-1B).

3. Glycogen degradation and synthesis (Chapter 17)

Glycogen, the storage form of glucose in animals, occurs mostly in liver and muscle. Its conversion to glucose-6-phosphate (G6P) for entry into glycolysis is catalyzed, in part, by glycogen phosphorylase, whereas the opposing synthetic pathway is mediated by glycogen synthase. These enzymes are reciprocally regulated through phosphorylation/dephosphorylation reactions as catalyzed by amplifying cascades that respond to the levels of the hormones glucagon and epinephrine through the intermediary of cAMP.

4. Fatty acid degradation and synthesis (Sections 23-1 through 23-5)

Fatty acids are broken down in increments of C_2 units through β oxidation to form acetyl-CoA. They are synthesized from this compound via a separate pathway. The activity of the β -oxidation pathway varies with the fatty acid concentration. This, in turn, depends on the activity of "hormone-sensitive" triacylglycerol lipase in adipose tissue that is stimulated, through cAMP-regulated phosphorylation/dephosphorylation reactions, by glucagon and epinephrine but inhibited by insulin. The fatty acid synthesis rate varies with the activity of acetyl-CoA carboxylase, which is activated by citrate and inhibited by the pathway product palmitoyl-CoA. Fatty acid synthesis is also subject to long-term regulation through alterations in the rates of synthesis of the enzymes mediating this process as stimulated by insulin and inhibited by fasting.

5. Citric acid cycle (Chapter 19)

The citric acid cycle oxidizes acetyl-CoA, the common degradation product of glucose, fatty acids, and ketogenic amino acids, to CO_2 and H_2O with the concomitant production of NADH and $FADH_2$. Many glucogenic amino acids can also be oxidized via the citric acid cycle through their breakdown to one of its intermediates (Section 24-3). The activities of the citric acid cycle regulatory enzymes, citrate synthase, isocitrate dehydrogenase, and α -ketoglutarate dehydrogenase, are controlled by substrate availability and feedback inhibition by cycle intermediates.

6. Oxidative phosphorylation (Chapter 20)

This mitochondrial pathway oxidizes NADH and $FADH_2$ to NAD^+ and FAD with the coupled synthesis of ATP. The rate of oxidative phosphorylation, which is tightly coordinated with the metabolic fluxes through glycolysis and the citric acid cycle, is largely dependent on the concentrations of ATP, ADP, and P_i .

7. Pentose phosphate pathway (Section 21-4)

This pathway functions to generate NADPH for use in reductive biosynthesis, as well as the nucleotide precursor ribose-5-phosphate, through the oxidation of G6P. Its flux-generating step is catalyzed by glucose-6-phos-

phate dehydrogenase, which is controlled by the level of NAD^+ . The ability of enzymes to distinguish between $NADH$, which is mainly utilized in energy metabolism, and $NADPH$ permits energy metabolism and biosynthesis to be regulated independently.

8. Amino acid degradation and synthesis (Sections 24-1 through 24-5)

Excess amino acids may be degraded to common metabolic intermediates. Most of these pathways begin with an amino acid's transamination to its corresponding α -keto acid with the eventual transfer of the amino group to urea via the urea cycle. Leucine and lysine are ketogenic amino acids in that they can be converted only to acetyl-CoA or acetoacetate and hence cannot be glucogenic precursors. The other amino acids are glucogenic in that they may be, at least in part, converted to one of the glucose precursors—pyruvate, oxaloacetate, α -ketoglutarate, succinyl-CoA, or fumarate. Five amino acids are both ketogenic and glucogenic. Essential amino acids are those that an animal cannot synthesize itself; they must be obtained from plant and microbial sources. Nonessential amino acids can be synthesized by animals via pathways that are generally simpler than those synthesizing essential amino acids.

Two compounds lie at the crossroads of the foregoing metabolic pathways: acetyl-CoA and pyruvate (Fig. 25-1). Acetyl-CoA is the common degradation product of most metabolic fuels, including polysaccharides, lipids, and proteins. Its acetyl group may be oxidized to CO_2 and H_2O via the citric acid cycle and oxidative phosphorylation or used to synthesize fatty acids. Pyruvate is the product of glycolysis, the dehydrogenation of lactate, and the breakdown of certain glucogenic amino acids. It may be oxidatively decarboxylated to yield acetyl-CoA, thereby committing its atoms either to oxidation or to the biosynthesis of fatty acids. Alternatively, it may be carboxylated via the pyruvate carboxylase reaction to form oxaloacetate, which, in turn, either replenishes citric acid cycle intermediates or enters gluconeogenesis via phosphoenolpyruvate, thereby bypassing an irreversible step in glycolysis. Pyruvate is therefore a precursor of several amino acids as well as of glucose.

The foregoing pathways occur in specific cellular compartments. Glycolysis, glycogen synthesis and degradation, fatty acid synthesis, and the pentose phosphate pathway are largely or entirely cytosolically based, whereas fatty acid degradation, the citric acid cycle, and oxidative phosphorylation occur largely in the mitochondrion. Different phases of gluconeogenesis and amino acid degradation occur in each of these compartments. The flow of metabolites across compartment membranes is mediated, in most cases, by specific carriers that are also subject to regulation.

The enormous number of enzymatic reactions that simultaneously occur in every cell (Fig. 15-1) must be coordinated and strictly controlled to meet the cell's needs. Such

regulation occurs on many levels. Intercellular communications regulating metabolism occur via certain hormones, including epinephrine, norepinephrine, glucagon, and insulin, as well as through a series of steroid hormones known as glucocorticoids (whose actions are discussed in Section 34-4A). These hormonal signals trigger a variety of cellular responses, including the synthesis of second messengers such as cAMP in the short term and the modulation of protein synthesis rates in the long term. On the molecular level, the enzymatic reaction rates are controlled by phosphorylation/dephosphorylation via amplifying reaction cascades, by allosteric responses to the presence of effectors, which are usually precursors or products of the reaction pathway being controlled, and by substrate availability. The regulatory machinery of opposing catabolic and anabolic pathways is generally arranged such that these pathways are reciprocally regulated.

2. ORGAN SPECIALIZATION

In this section we consider how the special needs of the mammalian body organs are met and how their metabolic capabilities are coordinated to meet these needs. In particular, we discuss brain, muscle, adipose tissue, and liver (Fig. 25-2).

A. Brain

Brain tissue has a remarkably high respiration rate. For instance, the human brain only constitutes ~2% of the adult body mass but is responsible for ~20% of its resting O_2 consumption. This consumption, moreover, is independent of the state of mental activity; it varies little between sleep and the intense concentration required of, say, the study of biochemistry. Most of the brain's energy pro-

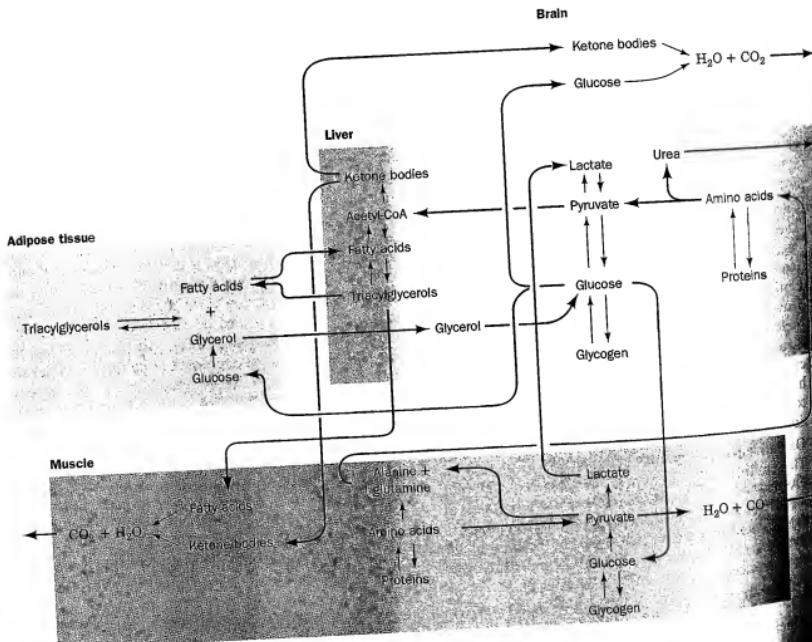


FIGURE 25-2. The metabolic interrelationships among brain, adipose tissue, muscle, and liver. The red arrows indicate pathways that predominate in the well-fed state when glucose, amino acids, and fatty acids are directly available from the intestines.

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inhibitor binds essentially irreversibly to any trypsin formed in the pancreas so as to inactivate it. Furthermore, the trypsin-catalyzed activation of trypsinogen (Fig. 14-26) occurs quite slowly, presumably because the unusually large negative charge of its highly evolutionarily conserved N-terminal hexapeptide repels the Asp at the back of trypsin's specificity pocket. Finally, pancreatic zymogens are stored in intracellular vesicles called **zymogen granules** whose membranous walls are thought to be resistant to enzymatic degradation.

Zymogens Have Distorted Active Sites

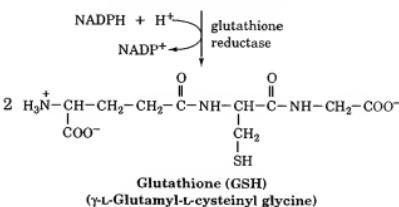
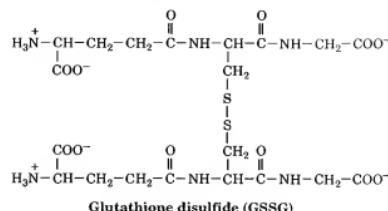
Since the zymogens of trypsin, chymotrypsin, and elastase have all their catalytic residues, why aren't they enzymatically active? Comparisons of the X-ray structures of trypsinogen with that of trypsin and of chymotrypsinogen with that of chymotrypsin show that upon activation, the newly liberated N-terminal Ile 16 residue moves from the surface of the protein to an internal position, where its free cationic amino group forms an ion pair with the invariant anionic Asp 194 (Fig. 14-21). Aside from this change, however, the structures of these zymogens closely resemble those of their corresponding active enzymes. Surprisingly, this resemblance includes their catalytic triads, an observation which led to the discovery that these zymogens are actually enzymatically active, albeit at a very low level. Careful comparisons of the corresponding enzyme and zymogen structures, however, revealed the reason for this low activity: *The zymogens' specificity pockets and oxyanion holes are improperly formed such that, for example, the amide NH of chymotrypsin's Gly 193 points in the wrong direction to form a hydrogen bond with the tetrahedral intermediate (see Fig. 14-25)*. Hence, the zymogens' very low enzymatic activity arises from their reduced ability to bind substrate productively and to stabilize the tetrahedral intermediate. These observations provide further structural evidence favoring the role of transition state binding in the catalytic mechanism of serine proteases.

4. GLUTATHIONE REDUCTASE

Lysozyme and the serine proteases all catalyze hydrolytic reactions. In contrast, the third enzyme that we shall consider in mechanistic detail, *glutathione reductase*, catalyzes an oxidation-reduction reaction. Such reactions are extremely important in metabolic processes. We have chosen to study glutathione reductase, which sequentially catalyzes several electron-transfer processes, because it is one of the few such enzymes in which the pathway of electron flow has been well characterized.

Glutathione reductase is a nearly ubiquitous enzyme that catalyzes the NADPH-dependent reduction of glutathione

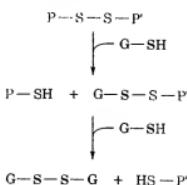
disulfide (GSSG) to glutathione (GSH):



(the structures of NADP⁺ and NADPH are indicated in Fig. 12-2). This process normally produces a GSH:GSSG ratio of over 100:1, which permits GSH to function as an intracellular reducing agent (the thermodynamics of oxidation-reduction reactions is discussed in Section 15-5). For example, the inactivation of proteins (P) that have free SH groups through the spontaneous oxidative formation of mixed disulfides



is reversed through disulfide interchange with GSH.



GSH also acts as a coenzyme in several enzymatically catalyzed reductions and plays an important role in the transport of amino acids into certain cells (Section 24-4C).

FAD Is an Essential Redox Coenzyme

Glutathione reductase contains the electron-transfer prosthetic group flavin adenine dinucleotide (FAD; Fig. 14-28). Flavins (substances that contain the isooxalazine ring) can undergo two sequential one-electron transfers (Fig. 14-28), or a simultaneous two-electron transfer that bypasses the semiquinone state. The glutathione reductase reaction involves the simultaneous transfer of two electrons so that

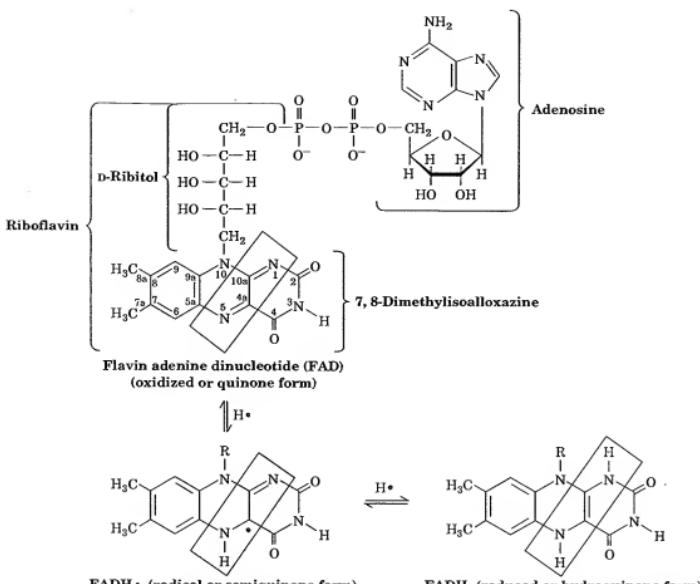


FIGURE 14-28. The molecular formula and reactions of the coenzyme flavin adenine dinucleotide (FAD). The term “flavin” is synonymous with the isoalloxazine ring system. The d-ribitol residue is derived from the alcohol of the sugar d-ribose. FAD may be half-reduced to the stable radical FADH[·] or fully

reduced to FADH₂ (boxes). Consequently, different FAD-containing enzymes cycle between different oxidation states of FAD. FAD is usually tightly bound to its enzymes so that this coenzyme normally is a prosthetic group rather than a cosubstrate as is the case, for example, with NAD⁺.

in this case, the FAD never assumes its radical form. The oxidation state of the flavin in a **flavoprotein** (flavin-containing protein) is readily established from its characteristic UV-visible spectrum: FAD is an intense yellow, whereas FADH₂ is pale yellow.

Humans and other higher animals are unable to synthesize the isoalloxazine component of flavins, so they must obtain this substance from their diets, for example, in the form of riboflavin (vitamin B₂) (Fig. 14-28). Riboflavin deficiency is quite rare in humans, in part because of the tight binding of flavin prosthetic groups to their apoenzymes. The symptoms of riboflavin deficiency, which are associated with general malnutrition or bizarre diets, include an inflamed tongue, lesions in the corners of the mouth, and dermatitis.

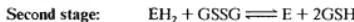
Glutathione Reductase Catalyzes a Two-Stage Reaction

Glutathione reductase from human erythrocytes is a dimer of identical 478-residue subunits that are covalently linked by an intersubunit disulfide bond. In the absence of

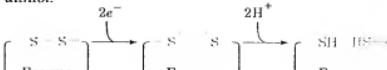
GSSG, the enzyme catalyzes the first stage of a two-stage reaction:



where E represents fully oxidized glutathione reductase and EH₂ is a stable two-electron reduced intermediate whose chemical nature we shall presently discuss. Upon subsequent addition of GSSG, EH₂ reacts to form products and complete the catalytic cycle.



The glutathione reductase reaction is more complex than these overall reactions suggest. Vincent Massey and Charles Williams demonstrated that *oxidized glutathione reductase (E)* contains a “redox-active” disulfide bond, which in EH₂ has accepted an electron pair through bond cleavage to form a dithiol.



APPENDIX B



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